which are partially or primarily mediated by direct contact of sertraline with the upper gastrointestinal tract, rather than being mediated systemically.

The delay can be a spatial delay, meaning that the dosage form is sensitive to its environment of use. Applicants independent claims 1, 14 and 21 are directed to spatially delayed dosage forms generally (claim 1), and to particular types of spatially delayed dosage forms such as pH-triggered dosage forms (claim 14) and enzyme-triggered dosage forms (claim 21).

The delay can also be temporal, meaning that the dosage form delays the release of sertraline for a set period of time which is not related to its position along the gastrointestinal tract. Independent claims 27 and 34 define such dosage forms.

Advantageously, Applicants provide a dosage form of sertraline which has a shorter Tmax, the time it takes for sertraline to reach its maximum value in the blood, than conventional immediate release sertraline dosage forms. This permits faster appearance of sertraline in the bloodstream, and a potentially faster therapeutic effect. A delayed release sertraline dosage form reflecting a decreased Tmax is defined in independent claim 41.

The Rejections

Claims 1, 6, 10, 11, and 14 stand rejected under 35 USC 102(b) over US patent 4,803,076 (hereinafter "Ranade"). The Examiner stated that

> The instant claims are directed to a delayed release oral dosage form comprising a core containing sertraline and a pharmaceutically acceptable salt thereof coated with a polymer that is substantially impermeable to sertraline at the pH of the stomach.
>
> Ranade disclose controlled release delivery systems comprising sertraline, and other desired excipients such as magnesium stearate or lactulose, and ethyl cellulose coated with methylene chloride solution of ethylene vinyl acetate copolymer and finally drying said tablets, wherein said tablets comprise multiple coats and dissolute in simulated intestinal fluid at a lower than 10% rate (see example 1 and 2 and 5 and figure 14 and 15). Thus Ranade meets the limitations set forth in the instant claims. [Page 2 of the Office Action]

The rejection is traversed on the basis that Ranade does not meet all of the elements of Applicants' claims and, therefore, by definition, cannot anticipate Applicants' claims. To anticipate a claim, a single source must contain all of the elements of the claim. Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 90 (Fed. Cir. 1986). Missing elements may not be supplied by the knowledge of one skilled in the art or by the disclosure of another reference. Stuctural Rubber Prods. v. Park Rubber Co., 223 USPQ 1264 (Fed Cir 1984). Ranade discloses a controlled release device substantially in the shape of a

truncated cone. Ranade is clearly related to a device exhibiting first order sustained release and discloses nothing relating to an initial period of delay. In fact, no delayed release component is disclosed at all. Ranade in fact teaches away from a device exhibiting delayed release in that Ranade discloses that the truncated cone has its top open for immediate exposure and access to the use environment, clearly providing no period of delay. See the opening paragraph of column 1, lines 10 to 22, where it is stated

> "Said device comprises said substance homogeneously disposed and contained substantially in the shape of a truncated cone by means of an impermeable wall or coating on the base and sides *(but not the top)* of said cone....the present invention is also directed to a tablet press for use in the manufacture of a tablet substantially in the shape of said truncated cone, and (after fully coating such tablets by conventional means) to an apparatus for *removal of the tablet coating from the top* (i.e., smaller diameter end) of the tablets." [Emphasis by bolding provided]

Ranade repeats the importance of having an open area on his device at column 3, lines 19-21:

"Finally, the impermeable coating is removed from the top of each cone shaped tablet,..."

The Ranade Examples referred to by the Examiner all clearly describe devices in which the coating is removed from the top of each device described. Since Ranade does not teach a device exhibiting an initial period of delay followed by immediate release, Ranade does not teach all the elements of Applicants' invention. Ranade, by teaching a device which exhibits first order sustained release, in fact teaches away from a device which (1) exhibits delayed release followed by immediate release, and (2) does not have a first order release component.

It is respectfully requested that the §102(b) rejection over Ranade be withdrawn.

Claims 1-53 stand rejected under 35 USC §102(b) as anticipated by or, in the alternative, under 35 USC 103(a) as obvious over WO 92/02212. The examiner stated

> The instant claims are directed to a delayed release oral dosage form comprising a core containing sertraline and a pharmaceutically acceptable salt thereof coated with a polymer that is substantially impermeable to sertraline at the pH of the stomach, but permeable at the PH of the small intestine. The instant claims are also directed to method of treating patients in needs of sertraline therapy.
>
> The international patent WO 92/02212 disclose the process of making a controlled release tablet or capsule comprising a core containing a therapeutic compound such as sertraline coated with a cellulose acetate or ethyl cellulose, and optionally a pore-forming material (see claims 1-2, 8, 10-13, 16, 20-25, examples 1-

3.) Therefore, WO 92/02212 meet the limitations set forth in the instant claims. [Pages 3-4]

The rejection is traversed on the basis that WO 92/02212 (hereinafter "Herbig") does not disclose, suggest, or motivate a delayed release device which, following the period of delay, effects immediate release of its remaining sertraline. Herbig discloses a pharmaceutical delivery device which exhibits sustained release. It comprise a core which in turn comprises an active substance surrounded by a porous substructure and one or more interfacial (IF) membranes. The porous substructure acts as a support for the IF membrane. The active substance(s) (and excipients, if any) are released from the device by either diffusion or osmotic pumping. Herbig neither discloses nor suggests anything relating to a device having an initial period of delay engineered into the device which, following the initial delay period, effects immediate release of the remaining active ingredient. Herbig discloses a sustained release device, and discloses no component of delay or immediate release. Thus it is not seen how Applicants' device which has a delay component and an immediate release component can be obvious over a reference which discloses neither component.

The Examiner's comments regarding cellulose acetate coatings is traversed and/or not understood. The cellulose acetate named in Herbig as a material for forming a thick porous substructure, and characterized by the Examiner as "pH-sensitive" is in fact not sensitive to pH, at least not to the pH conditions and/or changes occurring along the human gastrointestinal tract, and not to the in vitro tests described in Applicants' specification. Cellulose acetate is used in Herbig to form a non-degrading, non-dissolving coating which passes through the human body largely chemically unaffected. In fact, a person having ingested a capsule shell made of cellulose acetate generally ends up excreting the shell into the feces, this fact having been verified in human clinical trials.

The Examiner further likened cellulose acetate to

> "...natural polymeric coatings such as hydroxymethylcellulose that are used in the instant invention, and therefore, inherently capable of being degraded at the presence of intestinal enzymes." [Page 4 of the Office Action]

First, the Examiner's comments are not understood in that hydroxymethylcellulose is not mentioned in the instant invention. The cellulose derivatives disclosed at page 23, lines 6-7 are used in the instant invention as materials which form a water soluble coating for a temporally delayed device. Cellulose acetate, however, is not water soluble and is not subject to enzymatic degradation. Also, it is not understood how the Examiner has

concluded that "..said polymer [cellulose acetate] is pharmaceutically equivalent to natural coatings", or that his conclusion is well known in the art. The remarks are accordingly traversed for the reasons set forth above. It is requested that the comments be withdrawn as support for the rejection, and accordingly also respectfully requested that the rejection under §103(a) over Herbig be withdrawn in its entirety.

Claims 1-53 stand rejected under 35 USC §103(a) over Bechgaard (EP 0 080 341) in view of Drug Facts and Comparisons. The examiner stated:

> Bechgaard et al disclose methods of preparing pharmaceutical oral controlled release multiple-unit compositions comprising a core containing an active therapeutic agent such as an antidepressant...coated by a polymeric entity which is substantially resistant to gastric environment, but is erodible under the conditions in the small intestine.... Furthermore the oral controlled release of Bechgaard are coated with a coating that is selectively eroded in the distal part of the small intestine, and will preferably release at least 90% of the active substance with in one hour at a pH of 7.5 (see page 14, lines 8-16). Bechgaard et al, however, fail to specifically teach a sertraline containing enteric release dosage form.
>
> It is well known in the art that oral pharmaceutical preparations that are associated with upper gastric irritation may be formulated in the form on an enteric coated tablet to minimize GI side effects that are associated with direct GI irritation of such drugs. Further, serotonin reuptake inhibitors such as sertraline have been shown to cause about 1% GI related side effects such as hemorrhagic ulcer, stomatitis, and gastritis (see Facts and Comparison Page 1574 lines 16-20.) [Pages 5-6 of the Office Action]

The rejection is traversed on the basis that the references cited by the Examiner neither disclose nor motivate Applicants' invention. As stated at page 2, lines 20-24 of Applicants' specification, the locally mediated nature of sertraline GI side effects was not known prior to the human clinical studies disclosed in the application (see Example 2). Such side effects are not universally locally mediated for all drugs which elicit them. Thus, prior to this invention the art did not disclose that sertraline side effects were locally mediated, and thus could offer no expectation of success that delayed release sertraline, as defined in Applicants' claims, would remediate such side effects. It is only Applicants who have done that. Facts and Comparisons does nothing to remedy this defect in the art. It is well accepted that, even if the art appears combinable, particularly with the aid of hindsight, the art must still suggest the desirability of a modification. The mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 221 USPQ 1125 (Fed Cir 1984). Certainly, without a suggestion or disclosure based in the art that sertraline side effects are locally mediated, the art cited by the Examiner can not suggest the desirability of making Applicants' dosage forms.

Further, Bechgaard teaches coatings which dissolve in the distal part of the small intestine, i.e., near the colon. See Bechgaard , page 14, first two full paragraphs. For that, Bechgaard teaches an enteric coating which is substantially insoluble at a pH below 7, i.e., below a pH which is characteristic of the lower small intestine. This is in contrast to Applicants who disclose water solubility and/or water disintegrability for their coatings at a pH above 5.0 (page 11, first three lines). By this feature, Applicants' make possible dosage forms which will disintegrate at a pH of 6 to 6.5, which pH is characteristic of the upper small intestine. Bechgaard, by means of his requirement for an enteric coating which is substantially insoluble below a pH of 7 (see Bechgaard at page 14, lines 1-4) would permit little or no release at the lower pH of upper small intestine. In this respect, one following the teachings of Bechgaard would be led away from Applicants' invention.

In view of the above arguments, it is accordingly requested that the rejection over Bechgaard in view of Drug Facts and Comparisons be withdrawn.

In view of the foregoing comments and amendments, it is respectfully submitted that this application is in condition for allowance. A Notice of Allowance is courteously requested.

Respectfully Submitted,

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